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Calcium Channel Blockers Increase Sunitinib Effectiveness in Metastatic Renal Cell Carcinoma Treatment

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Abstract
Aim: Repurposing non-cancer drugs may be a new hope for cancer treatment. It has many advantages. Sunitinib is a tyrosine kinase inhibitor that inhibits vascular epithelial growth factor receptors. It is used for metastatic renal cell carcinoma (mRCC) treatment. We planned to investigate the effects of noncancer drugs like calcium channel blockers (CCBs) and others on sunitinib in mRCC patients.
Material and Methods: We retrospectively scanned the files of mRCC patients applied to our center between January 2013 and April 2019 and used sunitinib. We analyzed some parameters of these patients and their effects on overall survival (OS) and progression-free survival (PFS). A x2 or Fisher's exact test, Kaplan-Meier and Cox regressions were used in the statistical analysis.
Results: Thirty-five patients were examined, 15 of them were taking CCB for arterial hypertension and sunitinib for RCC, simultaneously. The 36-Months OS rates of CCB users and non-users were 61.1 and 38.9%, respectively (OR:5.1, 95% CI: 1.17-22.1, P=.041). The 24-Months PFS rates of CCB users and non-user were 68.8 and 31.3%, respectively (OR:8.25, 95% CI: 1.79-38.01, P=.007).
Discussion: It is a new idea to combine the targeted cancer drugs and non-cancer drugs for better anticancer outcomes. There were 36-months OS and 24-months PFS advantages with simultaneously taking CCBs and sunitinib. Sunitinib and CCBs combination should be studied in preclinical studies and their additive effect mechanisms should be clarified.

Keywords
Calcium Channel Blocker, Renal Cell Carcinoma, Repurposing, Sunitinib

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Introduction

Sunitinib is a multitarget tyrosine kinase inhibitor (TKI); it is mainly an antiangiogenic drug. Also, it has direct antitumoral and immune activator effects [1]. Sunitinib has been used in the treatment of metastatic renal cell carcinoma (mRCC) treatment since 2006. Sunitinib provided an advantage of approximately 5 months of overall survival (OS) and 6 months of progression-free survival (PFS) over interferon-alfa in mRCC [2]. While we can observe a very good survival advantage in some patients, we cannot see this advantage in others, and we don't know why. So far, there are no biomarkers predicting the efficacy of sunitinib. Can we do anything to increase the effectiveness of sunitinib? Repurposing a drug means using a drug out of its indication. Especially during the COVID-19 pandemic, drug repurposing studies have been carried out frequently. Repurposing non-cancer drugs for cancer is a popular issue nowadays, also. Repurposing has many advantages. We can save time and money while getting a reliable drug quickly. We recently showed that calcium channel blockers (CCBs) and erlotinib have additive effects in metastatic non-small cell lung cancer [3]. We also showed in another study that CCBs and regorafenib have additive effects in metastatic colorectal cancer [4]. We aimed to investigate whether CCBs and sunitinib have additive effects in mRCC.

Material and Methods

It was a retrospective study conducted on 35 metastatic RCC patients who received sunitinib, diagnosed between 2013 and 2019, admitted to our center. All patients enrolled in the study had pathologically confirmed clear cell histology and stage IV RCC. Patients not taking sunitinib were excluded. We noted the patient's clinical characteristics from their files. Data about the medications of the patients were recorded from their medical charts. We used descriptive statistics to show clinical characteristics (Table 1). Parameters that may affect the outcome of mRCC such as age, sex, comorbidities (hypertension [HT], and diabetes mellitus [DM]), and other medications including CCB, renin-angiotensin system inhibitor, proton pump inhibitor, inhaled steroid, insulin were noted. We analyzed the OS, which was defined as the time elapsed from the sunitinib starting date to the date of death from any cause or study termination date. Progression-free survival is defined as the time elapsed from starting sunitinib date to progression or study termination date. The follow-up time was defined as the time from the date of diagnosis to the date of death or the last follow-up date. The statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) version 22 (SPSS Inc, Chicago, IL). A univariate analysis was performed using the Kaplan–Meier method to estimate the OS of different patient groups, and the groups were compared with the log-rank test. Cox-regression analysis was used to determine the association of factors with the OS in the multivariate analysis. In the multivariate analysis, confounders were included if they were significant at a 0.05 level in the univariate analysis (log-rank test) or thought to be important for OS or the effect of the factors. The results were expressed as median OS, median PFS, and hazard ratios (HRs) with 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. Also, x2 or Fisher's exact test was used for statistical analysis. Ethical approval was obtained by the Ethics Committee of our center on 12.04.2019 with protocol number 2019/76.

Results

This study included 35 patients with metastatic RCC and who received sunitinib. There were 15 CCBs users (11 amlodipine, 3 nifedipine, 1 benidipine). The median age was 60 (40-85) years. The median follow-up time was 36.9 months for the entire group. Median OS was 20.8 (95% CI, 9.8 – 31.8) months, median PFS was 14.4 (95% CI, 8.5 – 20.3) months. The objec-

Table 1. Descriptive Characteristics of Patients

	N	%
Sex		
Male	27	77
Female	8	23
Age (median, range), year	60.0 (40-85)	
Survival status		
Alive	7	20
Exitus	28	80
The best response to treatment		
Complete reponse	2	6
Partial response	8	23
Stable disease	12	34
Progression	7	20
Not evaluated	6	17
Sunitinib received line		
I	10	29
II	25	71
Interferon-alpha treatment		
Yes	24	69
No	11	31
Concomitant antihypertensive		
User	21	60
CCBs	15	43
ACEi-ARB	8	23
Beta-blocker	9	26
Non-user	14	40
Concomitant PPI use		
Yes	23	34
No	12	66
Concomitant inhaled steroid use		
Yes	7	20
No	28	80
Diabetes mellitus		
Yes	9	74
No	26	26
Statin use		
Yes	4	11
No	31	89
Renal impairment		
Yes	24	12
No	11	44
Hypothyroidism		
Yes	18	49
No	17	51

ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, CCB: Calcium channel blocker

Table 2. Factors affecting overall survival in patients who received sunitinib (Kaplan-Meier test was performed)

	N	Univariate analysis		Multivariate analysis	
		The median OS (95% CI) (month)	p-value (Log-Rank)	Hazard ratio (95% confidence interval)	p-value
Sex					
Male	27	31.8 (0-121)	.80	8.30 (0.44-47.70)	.018
Female	8	55.6 (12.0-51.7)			
Age					
<65	20	64.0 (3.7-124.3)	.11		
≥65	15	25.2 (10.9-39.5)			
Sunitinib line received					
First-line	10	36.9	.37		
Second-line	25	31.8			
Concomitant use of antihypertensive drugs					
Yes	21	71.6 (46.4-96.8)	.02	0.05 (0.004-0.82)	.036
No	14	21.1 (3.5-38.6)			
Concomitant use of CCBs					
Yes	15	93.8 (31.5-156.2)	.03	78.63 (4.61-1332.1)	.020
No	20	24.0 (17.1-30.9)			
Concomitant use of ACE inhibitor					
Yes	8	36.1	.40		
No	27	18.4			
Concomitant use of beta-blocker					
Yes	9	18.4	.97		
No	26	20.8			
Concomitant PPI use					
Yes	23	25.2 (7.0-43.5)	.15		
No	12	59.7 (5.5-113.9)			
Concomitant use of inhaled steroid					
Yes	7	31.8	.93		
No	28	36.9			
Diabetes mellitus					
Yes	9	71.6 (24.9-118.3)	.18		
No	26	29.4 (13.2-45.6)			
Renal impairment					
Yes	24	59.7 (10.3-109.1)	.03	0.81 (0.16-4.02)	.790
No	11	12.7 (0-35.7)			
Hypothyroidism					
Yes	17	55.6 (0-124.9)	.22		
No	18	25.2 (12.1-38.3)			

ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, CCB: Calcium channel blocker, OS: Overall survival, PPI: Proton pump inhibitor.

Table 3. Factors affecting progression-free survival in patients taking sunitinib (Kaplan-Meier test was performed)

	N	Univariate analysis		Multivariate analysis	
		The median PFS (95% CI) (month)	p-value (Log-Rank)	Hazard ratio (95% confidence interval)	p-value
Sex					
Male	27	14.4	.52		
Female	8	11.2			
Age					
<65	20	18.5 (11.4-24.6)	.024	2.88 (1.25-6.64)	.013
≥65	15	9.1 (7.1-11.1)			
Sunitinib line received					
First-line	10	27.7 (0.78-54.7)	.025	3.50 (1.32-9.26)	.012
Second-line	25	11.8 (3.5-20.0)			
Concomitant use of antihypertensive drug					
Yes	21	15.2 (9.1-21.3)	.117		
No	14	9.1 (1.3-17.0)			
Concomitant use of CCBs					
Yes	15	18.5 (7.0-30.0)	.065	3.01 (1.32-6.85)	.008
No	20	8.8 (4.5-13.2)			
Concomitant use of ACE inhibitor					
Yes	8	15.5	.865		
No	27	14.4			
Concomitant use of beta-blocker					
Yes	9	11.2	.968		
No	26	14.4			
Concomitant PPI use					
Yes	23	14.4	.893		
No	12	12.5			
Concomitant inhaled steroid use					
Yes	7	8.8 (4.0-13.6)	.23		
No	28	15.0 (10.6-19.4)			
Diabetes mellitus					
Yes	9	18.5 (8.2-28.8)	.182		
No	26	11.8 (3.0-20.5)			
Renal impairment					
Yes	24	15.0 (10.3-109.1)	.177		
No	11	9.9 (0-35.7)			
Hypothyroidism					
Yes	17	14.4	.927		
No	18	12.5			

Abbreviations. ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, CCB: Calcium channel blocker, OS: Overall survival, PPI: Proton pump inhibitor.

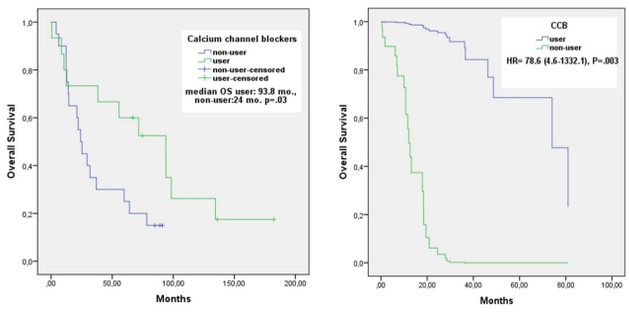

Figure 1. Effects of CCB on OS in those receiving sunitinib for mRCC (Kaplan-Meier and Cox Regression Model Curves)
CCB: Calcium channel blocker, HR: Hazard Ratio, Mo: Months, mRCC: Metastatic renal cell carcinoma, OS: Overall survival

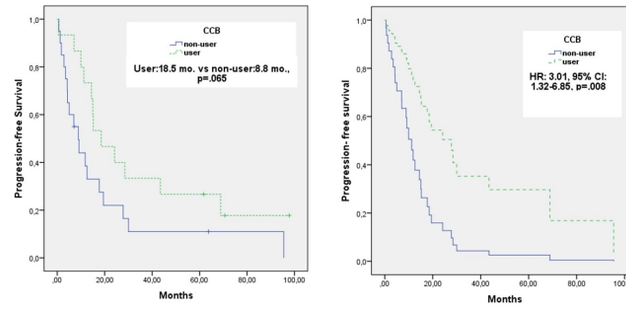

Figure 2. Effects of concomitant administration of sunitinib and CCB on PFS in mRCC (Kaplan-Meier Curves)
CCB: Calcium channel blocker, HR: Hazard Ratio, Mo: Months, mRCC: Metastatic renal cell carcinoma, PFS: Progression-free survival

tive response rate was 29%. The patient characteristics and their effects on OS and PFS are summarized in Table 2 and Table 3, respectively.

Calcium channel blocker taking (93.8 vs 24.1 months, p=0.03), renal impairment (59.7 vs 12.7 months, p=0.03) significantly improved OS in the univariate analysis, ACE inhibitor and beta-blocker using numerically improved OS but not statistically meaningful. After adjusting multivariate analysis CCB taking significantly improved OS (HR: 78.63, 95% CI: 4.61-1332.1, p=.03). In multivariate analysis, renal impairment did not improve OS (HR: 0.81, 95% CI: 0.16-4.02). Taking any type of anti-hypertensive drug improved OS in univariate analysis but it reduced OS in multivariate analysis (HR: 0.2, 95 CI: 0.004-0.82, p=0.03). Effects of CCB using on OS showed the Kaplan-Meier and Cox-regression curves in Figure 1.

Patients who were younger than 65 years old (18.5 mo. vs 9.1 mo., p=.024) received sunitinib as first-line treatment (27.7 mo. vs 11.8 mo., p= .025) had a better median PFS in univariate analysis. Calcium channel blocker users had numerically improved median PFS in the univariate analysis, but it was not statistically meaningful (18.5 vs 8.8 months, p=.065). After adjusting multivariate analysis, CCB users had significantly improved median PFS (HR: 3.01, 95% CI: 1.32-6.85, p=.008). Effects on median PFS of CCB taken concomitantly with sunitinib showed the Kaplan-Meier curves in Figure 2. In multivariate analysis, patients who were younger than 65 years old (HR: 2.88, 95% CI: 1.25-6.64, p=.013) and who received sunitinib at first-line (HR: 3.5, 95% CI: 1.32-9.26, p=.012) had better PFS.

Also, CCB users and non-users were compared in terms of 36-months OS and 24-months PFS rates. The 36-Months OS rates of CCB users and non-users were 61.1 and 38.9%, respectively (OR:5.1, 95% CI: 1.17-22.1, p=.041). The 24-Months PFS rates of CCB users and non-user were 68.8 and 31.3%, respectively (OR:8.25, 95% CI: 1.79-38.01, P=.007).

Discussion

This retrospective study showed that CCBs and sunitinib have powerful additive effects in mRCC. In multivariate analysis, CCB users have statistically meaningful better OS and PFS compared to non-users. There are nearly 2-fold better 36-months OS (61 vs 38%), 24-months PFS rates (68 vs 31%) of CCB users.

Drug repurposing in cancer has many advantages. For example, CCBs already have sufficient safety, toxicity, and pharmacological data. Drug repurposing reduces the risk of clinical trial failure [5]. Developing a new anticancer drug needs a lot of money and time [6]. Are these additive effects of sunitinib and CCBs come from pharmacokinetic or pharmacodynamic features? No drug interactions have been previously reported with sunitinib and amlodipine. A study reported that amlodipine did not change the plasma concentration of sunitinib [7]. So, what is the mechanism of the additive anticancer effect of these drugs?

Calcium plays role in protein phosphorylation, enzyme regulation, gene transcription, and translation. Calcium channels in the cell membrane and endoplasmic reticulum maintain the calcium balance between the inside and outside of the cell. There are two major calcium channel categories: voltage-gated channels and non-voltage-gated channels. L, P/Q, N, R, and T types are the subtypes of voltage-gated calcium channels. Recently, an increasing number of articles have been published about tumorigenesis and tumor progression role of calcium channels [8]. Dihydropyridines (amlodipine, nicardipine, etc.), verapamil, and diltiazem are all L-type CCBs. Some preclinical and clinical studies reported antitumoral effects of L-type CCBs. In a study, CCBs had shown antitumoral activity on some of 578 human cancer cell lines [9]. Tingle et al. showed that metastatic pancreatic cancer patients who had previously been prescribed L-type CCBs for hypertension had numerically better OS (15.3 vs. 10.1 months, p=.131) [10]. Altered calcium channels play roles in colon tumorigenesis and breast cancer pathogenesis [11, 12]. N-type calcium channel facilitates the progression of NSCLC, blocking this channel inhibits the progression [13]. Marwa H et al. reported that T-type CCBs strengthen the anticancer effects of cisplatin-etoposide combination in in-vitro tests [14]. Also, CCBs can alter the tumor microenvironment and this may be another possible mechanism of anticancer action [8]. Phosphatidylinositol triphosphate kinase-Akt pathway plays a role in some cancer types and CCBs can inhibit this pathway, which may be another anti-cancer mechanism [13].

It is a new idea to combine the targeted cancer drugs and non-cancer drugs for better anti-cancer outcomes. Numerous articles have shown the relationship between calcium channels and cancer. In our study, we showed that taking CCB improves the median OS and PFS with sunitinib, in mRCC. The limitations are that the number of patients included in the study was small and it was a retrospective study. Larger and prospective studies need to show that CCB and sunitinib combinations can be used in mRCC treatment.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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